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## Growth Characteristics in individuals with Osteogenesis Imperfecta in North America - Results from a Multicenter Study

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### Abstract

**Purpose**—Osteogenesis imperfecta (OI) predisposes to recurrent fractures, bone deformities, and short stature. There is a lack of large-scale systematic studies that have investigated growth parameters in OI.

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**Methods**—Using data from the Linked Clinical Research Centers, we compared height, growth velocity, weight, and body mass index (BMI) in 552 individuals with OI. Height, weight, and BMI were plotted on the Centers for Disease Control normative curves.

**Results**—In children, the median Z-scores for height in OI types I, III, and IV were  $-0.66$ ,  $-6.91$ , and  $-2.79$ , respectively. Growth velocity was diminished in OI types III and IV. The median Z-score for weight in children with OI type III was  $-4.55$ . The median Z-scores for BMI in children with OI types I, III and IV were  $0.10$ ,  $0.91$  and  $0.67$ , respectively. Generalized linear model analyses demonstrated height Z-score positively correlated with severity of OI subtype ( $p<0.001$ ), age, bisphosphonate use, and rodding ( $p<0.05$ ).

**Conclusions**—From the largest cohort of individuals with OI, we provide median values for height, weight, and BMI Z-scores which can aid in evaluation of overall growth in the clinic setting. This study is an important first step in the generation of OI-specific growth curves.

### Keywords

Osteogenesis Imperfecta; natural history study; growth; height; weight

## INTRODUCTION

Osteogenesis imperfecta (OI), a group of Mendelian disorders of connective tissue, predisposes to recurrent fractures, bone deformities, and short stature<sup>1</sup>. Nearly 90% of individuals with OI have pathogenic variants in *COL1A1* and *COL1A2* that encode for the  $\alpha 1$  and  $\alpha 2$  chains of type I collagen, a major protein of the bone matrix<sup>2</sup>. Over the past decade, discovery of numerous genes as causes for OI has underscored the genetic heterogeneity of this disorder. However, the Sillence classification, which was proposed well before the genetic basis of OI was known, continues to be used for management and counseling purposes<sup>3</sup>. Accordingly, the autosomal dominant, type I collagen related-OI is classified into non-deforming (type I), perinatally lethal (type II), progressively deforming (type III), and common variable (type IV) forms.

Short stature is a hallmark of the moderate-to-severe forms of OI. Previous studies have demonstrated that the mean birth length and weight in individuals with OI are below the normative data from the general population<sup>4,5</sup>. Whereas final height is significantly restricted in those with OI types III and IV, even those with milder forms of disease, i.e., type I, have reductions in the overall height as compared to the general population<sup>5-8</sup>. To date, only few studies have systematically analyzed the growth parameters in OI. Most reports are limited either by the size of the cohort or the lack of data on adults with OI<sup>5,6,8-13</sup>. In fact, there are only two studies outlining the growth parameters in both children and adults with OI<sup>7,8</sup>. The largest cohort with both children and adults with OI described to date (144 children and 199 adults) revealed that in addition to decreased height, obesity was common in OI<sup>7</sup>. Detailed assessments of anthropometric measures in OI can have both diagnostic and management implications. Appropriate characterization of the growth parameters can help identify affected individuals who are not meeting the expected growth patterns and institute lifestyle modifications for weight control.

In this report, we analyzed the cross-sectional growth parameters in a large cohort of individuals with OI from across North America (n=552; 408 children and 144 adults) who were enrolled in the observational study “Longitudinal Study of Osteogenesis Imperfecta” that was conducted by the OI Linked Clinical Research Centers (LCRC)<sup>14</sup>. The large sample size of the cohort allowed us to examine growth parameters in the various subtypes of OI and assess the potential correlations between height and the type of OI, surgical rodding, and bisphosphonate use.

## MATERIALS AND METHODS

### Study Population

The details about LCRC and the Longitudinal Study of Osteogenesis Imperfecta have been previously described<sup>14</sup>. The LCRC, comprised five clinical: Baylor College of Medicine (Houston, TX), Kennedy Krieger Institute (Baltimore, MD) with Nemours/Alfred I. DuPont Hospital for Children (Wilmington, DE), Oregon Health and Science University (Portland, OR), Shriners Hospital for Children (Chicago, IL), and Shriners Hospital for Children (Montreal, QC). The data collected from these clinical sites were coordinated and managed by the NIH Rare Disease Clinical Research Network’s (RDCRN) Data Management and Coordinating Center at the University of South Florida College of Medicine. The Collagen Diagnostic Laboratory at the University of Washington served as the center for molecular and biochemical analyses. The respective Institutional Review Boards of participating clinical sites approved the study. Informed consent was obtained from all subjects or their legal guardians.

At the clinical sites, demographic data, medical history, anthropometric measures of height, weight, and arm-span were collected and recorded in a uniform fashion by trained personnel. Height, weight, and arm-span were recorded as single measurements. The data were collected at every clinical site in accordance to the instructions outlined in the Manual of Operations and were reported using online case report forms.

- *Height*, defined as the vertical distance between crown of head and soles of feet, was measured using a wall-mounted stadiometer and recorded to the nearest 0.1 cm. When participants could not stand, supine length was measured from the heels to the top of the head.
- *Weight* was measured on an upright calibrated digital or beam scale to the nearest 0.1 kg. In individuals who were too young to stand alone, infant scale was used. When children could not stand on the scales, they were weighed while being held by a parent and weight of the child was calculated by subtracting the weight of the parent from the total weight. Body mass index (BMI) was calculated as weight in kg/ (height in m)<sup>2</sup>.
- *Arm span* was measured as the distance from one furthestmost fingertip to the other furthestmost fingertip when the participant’s arms were stretched out horizontally using a non-stretching long measuring tape to the nearest 0.1 cm. Arm span was measured in a single measure and not in parts which were then added together.

Overall, 552 participants were enrolled; this included 244 with OI type I, 110 with OI type III, 150 with OI type IV, 15 with OI type V, 12 with OI type VI, 5 with OI type VII, and 16 with an unclassified type (Table 1). The classification of OI was based on clinical features outlined in the Manual of Operations; however, genotypic information was used to reclassify patients when available. Data collected for analyses included age at enrollment, sex, OI type, family history of OI, history of bisphosphonate use (yes or no), history of rodding (yes or no), self-reported parental height, subject height, weight, and arm span. To analyze height within particular genotypes, we classified the type I collagen mutations as glycine substitution mutations within the triple helix domain (n=160), loss of function (nonsense, deletion, frameshift or splicing; n=144) mutations, and non-glycine missense variations (n=9). Given the small number of individuals with OI types V, VI and VII, they were excluded from further formal statistical evaluations. The height, weight, and BMI data presented here were collected at the initial enrollment visit.

### Statistical analysis

For participants below 20 years (OI type I, n=163; OI type III, n=83; OI type IV, n=123), the Centers for Disease Controls (CDC) growth curves were utilized to plot the height, weight, and BMI. The Z-scores were calculated using the L, M, S parameters based on the methodology described previously<sup>15</sup>. The Z-scores were computed using the AGD library in R. For comparison of Z-scores for height, weight, and BMI, between the OI types, Komogrov-Smirnov test was performed to evaluate for normal distribution; ANOVA or ANOVA on ranks were used as appropriate. When comparing Z-scores for height, weight, and BMI between OI types, we categorized individuals into age groups of 0–5 years, 5–10 years, 10–15 years, 15–20 years, and above 20 years. Z-scores for height and weight for individuals above 20 years of age were calculated using normative values from 20 year-old individuals. The differences in proportions of individuals below the 3<sup>rd</sup> percentile for height and weight between the OI types were analyzed using Fisher exact tests. For adult participants in the study (OI type I, n=81; OI type III, n=27 ; OI type IV, n=27) expected mid-parental height was calculated from self-reported parental heights and 5 cm was considered as one standard deviation from the mean as previously published<sup>16</sup>. The differences in proportions of individuals with final heights below 2 standard deviations from the expected height were analyzed using Fisher's exact test. The growth velocity between OI subtypes was assessed and the proportion of individuals falling outside of 2 standard deviations from the mean based on normative data were ascertained<sup>17</sup>.

To further evaluate the potential effects of age, history of orthopedic rodding, history of bisphosphonate use, and sex on height, we performed generalized linear model (GLM) analyses using backward elimination strategy with the 'step' function in R. The height Z-score was the dependent variable while the independent categorical variables included OI type (type I, III, or IV), sex (male or female), history of rodding (yes or no), and history of bisphosphonate therapy (yes or no); age was included as a continuous numeric variable. *P* values were calculated using the likelihood ratio test and correlations present with  $p < 0.05$  were tested for evidence of interaction.

The arm span to height ratio between OI subtypes were compared by one-way ANOVA among the age groups <10 years, 10–20 years, and >20 years. These age categories were chosen based on previous normative data that show increase in arm span to height after 10 years of age <sup>18</sup>.

## RESULTS

The characteristics of individuals enrolled in the study are outlined in Table 1. The autosomal dominant forms of type I collagen-related OI accounted for over 90 percent of all enrolled individuals.

### Height in OI

In the pediatric population (age < 20 years), the median (interquartile range or IQR) Z-scores for height in OI types I, III, IV, V, and VI were –0.66 (–1.43 to –0.02), –6.91 (–8.41 to –5.17), –2.79 (–3.95 to –1.69), –1.65 (–2.16 to –0.77), and –1.72 (–2.36 to –1.38), respectively (Figure 1). For the type I collagen-related OI, as expected, across all age groups, individuals with OI type III had diminished height compared to OI type I and OI type IV, and individuals with OI type IV had decreased height compared to OI type I ( $p<0.05$ ) (Figure 1). When plotted on the CDC growth curves, 9.5% of males and 18.1% of females with OI type I, 97.4% of males and 95.5% of females with OI type III, and 70.4% of males and 68.9% of females with OI type IV were below the third percentile for height (Figure 2). The odds ratio (95% confidence interval or CI) for being below the third percentile was 219 (50.5–953.4) for OI type III ( $p<0.001$ ) and 11.7 (6.5–20.9) for OI type IV ( $p<0.001$ ) as compared to type I. For OI type III the odds ratio for being below the third percentile was 18.76 (4.37–80.45) as compared to OI type IV ( $p<0.001$ ).

In adults with OI, the median (IQR) Z-scores for height were –1.10 (–1.90 to –0.38), –8.67 (–9.99 to –6.85) and –3.58 (–5.88 to –2.30), in OI types I, III, and IV, respectively. Pairwise comparisons revealed significant differences between OI subtypes ( $p<0.05$ ). In adults without a family history of OI, we calculated the expected mid-parental height based on self-reported parental height. The final adult height was affected in all OI subtypes with 48% with OI type I, 100% with OI type III, and 58% with OI type IV below 2 standard deviations from the expected mid-parental height. Fisher's exact test demonstrated a severe diminishing of final adult height for type III as compared to type IV OI ( $p<0.001$ ) and type I OI ( $p<0.01$ ); however, no statistically significant difference was noted between OI types I and IV.

We correlated the height Z-scores to mutation type in individuals who had demonstrated pathogenic variants in either *COL1A1* or *COL1A2*. For individuals with glycine substitution mutations, the median height Z-score (IQR) was –4.7 (–6.7 to –2.1), for individuals with other missense variants the median was –3.5 (–1.7 to –5.2) and for loss of function variants the median was –1.28 (–2.2 to –0.72). Height was significantly diminished in individuals with glycine substitutions compared to loss of function ( $p<0.001$ ). Furthermore, we examined whether different glycine substitutions had an effect on height. Individuals with glycine-to-serine substitutions had a median height Z-score of –5.6 (–6.7 to –3.1), whereas the median heights in glycine-to-aspartate and glycine-to-another amino acid were –3.5

(−5.5 to −3.2) and −3.2 (−6.8 to −1.7), respectively. While the median was lower for glycine to serine substitutions, this difference did not reach statistical significance.

### Growth Velocity in OI

We utilized the longitudinal aspect of the cohort to examine growth velocity in participants between the ages 3 and 16 years. We selected individuals that had at least two height measurements that were separated by 6 to 18 months. The velocity of growth was calculated as cm/year and the value obtained was plotted against normative data. In individuals with three or more measurements, the value between two consecutive measurements were considered as distinct data points and thus plotted separately. In total, there were 127 individuals with OI type I (n=61 male; n=66 female; n=259 growth velocity measurements), 46 individuals with OI type III (n=20 male; n=26 female, n=79 growth velocity measurements), and 76 individuals with OI type IV (n=37 male, n=39 female, n=148 growth velocity measurements) that were included in these analyses. In OI type I, 12.4% of growth velocities (32/259) were 2 standard deviations below the mean or lower for growth velocity whereas in OI types III and IV, this proportion was 51.9% (41/79), and 31.1% (46/148), respectively. This corresponds to increased odds ratio (95% CI) of having diminished growth velocity of 7.65 (4.30–13.61) in OI type III compared to type I, and of 3.20 (1.92–5.32) in OI type IV compared to type I ( $p<0.0001$ ).

### Weight in OI

The median (IQR) Z-scores for weight in the pediatric population in OI types I, III, IV, V, and VI were −0.41 (−1.14 to 0.56), −4.55 (−6.40 to −2.85), −1.55 (−2.37 to −0.31), −0.31 (−1.81 to 0.32) and −0.99 (−1.68 to 0.08), respectively (Supplementary Figure 1). ANOVA on ranks demonstrated significant differences between the OI subtypes across all age groups with weight in OI type III being significantly lower than in OI types I and IV ( $p<0.05$ ). We observed significant differences for weight between OI type IV and OI type I only in age groups of 0–5 years and 10–15 years ( $p<0.05$ , Supplementary Figure 1). As in height, a similar relationship was seen for weight where 11.8% males and 16.9% of females with OI type I, 35.8% of males and 33.3% of females with OI Type IV, and 94.7% of males and 84.8% of females with OI type III were below the third percentile ( $p<0.001$ ; Figure 3). The odds ratio (95% CI) for being below the third percentile was 43.20 (19.50–95.69) for OI type III ( $p<0.001$ ) and 15.76 (7.32–33.95) for OI type IV ( $p<0.001$ ) as compared to type I. For individuals with OI type III compared to OI type IV, the odds ratio for being below the third percentile was 2.74 (1.52–4.94) ( $p<0.005$ ).

### BMI in OI

The median (IQT) of Z-scores for BMI in the pediatric population in OI types I, III, IV were 0.10 (−0.58 to 0.94), 0.91 (0.42 to 1.61) and 0.67 (−0.18 to 1.33) (Supplementary Figure 2). When BMI was calculated by using measured height, individuals with OI type III had increased BMI as compared to OI types I and IV in adults and in children in the age groups 5–10 years and 15–20 years ( $p<0.05$ ; Figure 4 and Supplementary Figure 2).



### Arm span to height ratio in OI

The arm span to height ratio is an indicator of the relative severity of linear growth abnormalities of the axial and/or lower limb as compared to the upper limbs. The adult arm span is typically 5 cm greater in males and 2 cm greater in females as compared to height<sup>18</sup>. Arm span/height ratio changes with age wherein arm span is less than height in early childhood, equal to height by about 10 years in males and 12 years in females, and greater than height thereafter<sup>18</sup>. Thus, we compared the arm span/height ratio in age groups of <10 years, 10–20 years, and >20 years. Only in the >20 years group, we observed significant increased arm span/height in OI types III and IV compared to type I ( $p<0.001$  and  $p<0.05$ , respectively) (Supplementary Figure 3).

### Potential correlates affecting height in OI

Previous studies have shown that individuals with severe forms of OI can have “flattening” of their height curves so that the height Z-scores worsen with age<sup>7,8</sup>. With the widespread use of bisphosphonates, the effect of the medications on linear growth has been assessed in short-term studies without conclusive answers<sup>19–23</sup>. In order to understand the correlations between some co-variables and the height Z-scores, we performed a GLM analyses. As expected, OI subtype had a strong correlation with the height Z-scores through all pediatric ages ( $p<0.001$ ). Increasing age correlated with reduced height Z-scores ( $p<0.05$ ). Independent correlations were also observed for history of rodding ( $p<0.01$ ) and use of bisphosphonates ( $p<0.05$ ), where both of these co-variables correlated with overall reduced Z-scores. However, there were significant interactions between the OI subtype, history of rodding and bisphosphonate use. Thus, we could not independently assess the effects of these covariates on height.

## DISCUSSION

OI is a clinically heterogeneous disorder characterized by increased predisposition to recurrent fractures and bone deformities<sup>3</sup>. Whereas it is well recognized that growth deficiency can be found in patients with severe forms of OI, there is a lack of large-scale studies on growth parameters in various subtypes of OI. In this study, we have included the largest cohort of children and adults with OI from multiple clinical centers in North America.

The height measurements in this cohort are consistent with the expected phenotypes in OI and the growth patterns that were observed in other studies<sup>3,5–8</sup>. Height in OI type III is more severely affected as compared to OI types I and IV. Whereas some individuals with OI type I and IV can have heights within the normal ranges, the overall adult height is affected in all subtypes. Even in OI type I, the mildest form, the final height in nearly half of individuals is 2 standard deviations below the expected mid-parental height. Given these distinct patterns of height, height Z-scores could be utilized for clinical classification of type I collagen-related OI.

The etiology for short stature in OI is multifactorial. Scoliosis, kyphosis, vertebral fractures, recurrent long bone fractures, and bone deformities are important contributing factors. The



incidence of scoliosis and the rate of progression of curvature are significantly higher in the more severe forms of OI<sup>24</sup>. In a retrospective study of over 300 children with OI, Anissipour and colleagues found that the rates of progression of scoliosis were 6°, 4°, and 1°, in OI types III, IV, and I, respectively. The spinal deformities in the severe forms of OI can lead to reduction in truncal height. Similarly, fractures and bowing of femur and tibia, fractures occurring through the growth plates, and abnormalities of the epiphyses in the severe forms of OI lead to decreased limb length and overall height. The varying severity of involvement of the axial and appendicular skeleton can be reflected by the arm span to height ratio. In this study, we observed that arm span to height ratio, was increased in adults with types III and IV OI as compared to type I. These results are consistent with previous observations by Lund and colleagues and Aglan and colleagues<sup>6,8</sup>. Collectively, these findings suggest that truncal height is relatively more reduced than the length of the long bones in the more severe forms of OI.

However, clinical experience and previous studies have demonstrated that the overall height can be affected even in individuals without significant bone deformities<sup>7,8</sup>. Thus, it has been hypothesized that the primary matrix and cellular abnormalities may have a role in the decreased growth rates in OI. Decreased responsiveness to growth hormone/insulin-like growth factor 1 has been suggested as one of the mechanisms in few studies<sup>25,26</sup>. More recently, it was discovered that excessive transforming growth factor-beta (TGF-β) signaling is an important driver of the bone and extra-skeletal abnormalities in moderate-to-severe forms of OI<sup>27</sup>. The collagen over modification in severe forms of OI affects the interaction of type I collagen with small leucine-rich proteoglycans that bind TGF-β and thus results in increased availability of the ligand<sup>27–30</sup>. Increased TGF-β signaling in the growth plate could affect bone growth. In a mouse model of deficiency of E-selectin ligand, a negative regulator of TGF-β, Yang and colleagues demonstrated reduced chondrocyte proliferation and delayed terminal differentiation<sup>31</sup>. Thus, it is possible that increased TGF-β signaling could contribute to the abnormal growth in OI. While final adult height is affected across all types of OI, using the longitudinal nature of the data set, we also demonstrate that the growth velocity is affected. Current information on growth velocity in OI patients is rather limited, and studies that have addressed this have done in the context of therapy<sup>11,32,33</sup>. It is not known whether the decreased growth velocity in OI type III and IV is driven by the recurrent fractures or intrinsic abnormalities of the bone and cartilage.

Bisphosphonates are currently considered a standard-of-care and are widely used for the treatment of individuals with OI<sup>19–23,33–37</sup>. Whereas the effects of bisphosphonates on fracture risk in OI are difficult to address, the results have been inconclusive<sup>19–23,33–37</sup>. Few studies have addressed the effects of bisphosphonates on height in OI. Zeitlin and colleagues showed that 4 years of therapy with pamidronate increased height Z-scores in children with moderate-to-severe OI<sup>11</sup>. Similarly, it has also been shown that bisphosphonate therapy decreases the rate of progression of scoliosis in type III OI, if treatment is started before the age of six years<sup>24</sup>; however recent meta-analyses have not shown a significant effect of bisphosphonates on height<sup>38,39</sup>. In this study, we tried to find correlations between height Z-scores and the use of bisphosphonates. In our cohort, 30% of individuals with OI type I, 84% with OI type III, and 76% with OI type IV had received IV bisphosphonate at some time and 15% had received oral bisphosphonates in each subtype. However on GLM

analyses, there was a significant interaction between the OI subtype and the use of bisphosphonates, and the proportion of individuals with severe OI who were naïve to bisphosphonates was very low precluding independent assessment of the effect of bisphosphonates on the height.

Weight in OI has not been studied as extensively as height. In this report, we observed that individuals with OI type III continue to fall below third percentile of the CDC growth curves across all age groups. These results are consistent with the previous publications that report underweight in individuals with severe OI<sup>6</sup>. However, in spite of the lower weight, calculated BMI in OI tends to be higher, especially in OI type III. Using peripheral quantitative computed tomography, Palomo and colleagues have shown that the fat cross sectional area at the forearm in individuals with OI is similar to the control population<sup>40</sup>. These data imply that “increased BMI” is a result of the small value of the denominator during calculation and may not portend increased metabolic risks. It may thus be more important and practical to monitor serial weight in OI, especially in adults. Future studies that systematically measure body composition in OI may be helpful in risk stratification and further management.

Disorder-specific growth charts can be very helpful in monitoring growth in the clinic. To our knowledge, the only growth charts that have been developed in OI are for OI type I<sup>13</sup>. One challenge in creating standard growth charts for all subtypes of OI is the great variability in the clinical presentations. The experience gained for the studies in the OI LCRC was pivotal in establishing the Brittle Bone Disorders Consortium (BBDC). The data being collected in the BBDC would be helpful in generating OI-specific growth curves for all subtypes of OI.

In summary, our analyses of the largest cohort of individuals with OI demonstrates that individuals with severe forms of OI have reduced height as well as weight as compared to those with type I OI. This important study would be a significant first step in the construction of growth curves in this disorder.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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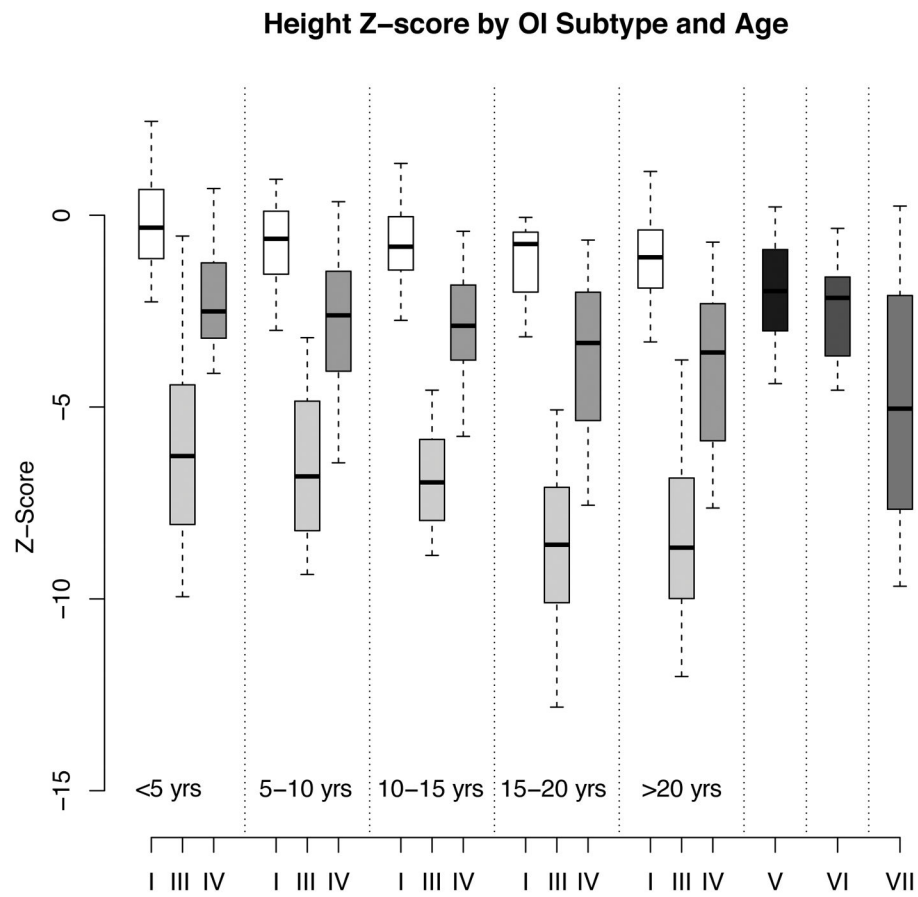
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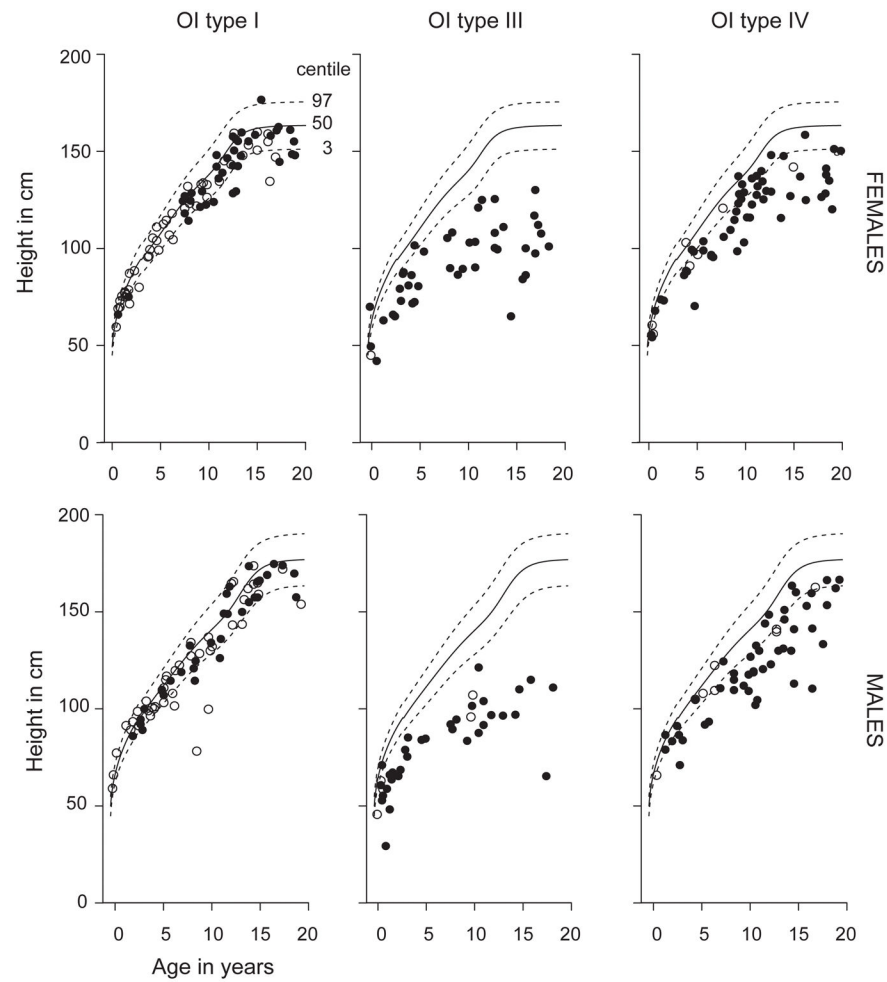
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**Figure 1. Height Z-scores in OI**

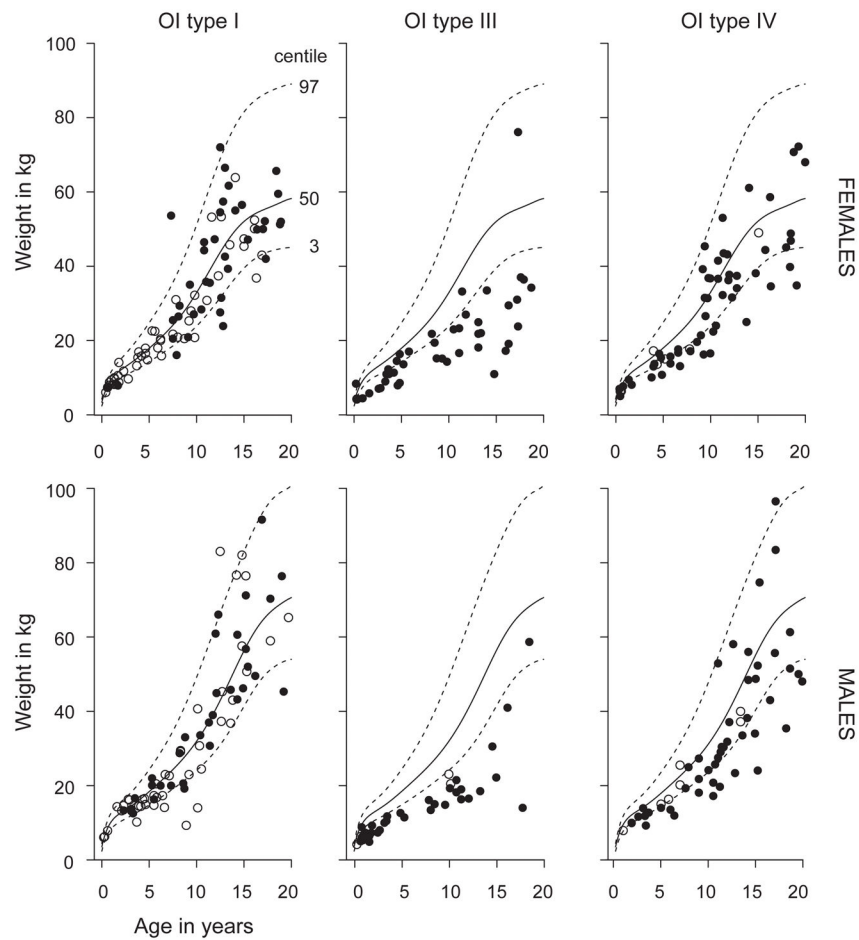
Box plots showing the median and the IQR for height Z-scores in the various age groups in type I collagen-related OI demonstrate significantly lower Z-scores in individuals with OI type III and type IV as compared to OI type I. The number of participants in types V, VI, and VII were limited and the pooled data have been represented.



**Figure 2.**

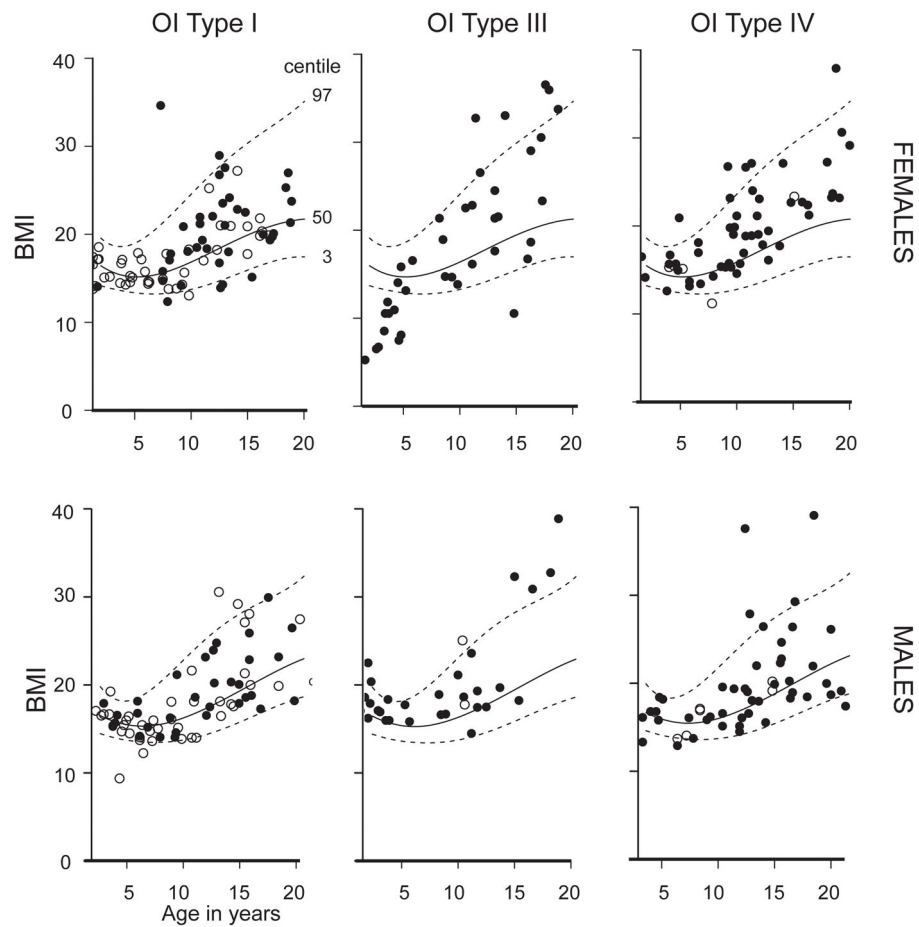
Cross sectional height measurements for participants in the cohort plotted on the CDC growth curves. Each circle represents one participant. Open circles represent individuals who were naïve to bisphosphonate treatment while black circles represent individuals who have received bisphosphonate at some point in their life.





**Figure 3.**

Cross sectional weight measurements for participants in the cohort plotted on the CDC growth curves. Each circle represents one participant. Open circles represent individuals who have naïve to bisphosphonate treatment while black circles represent individuals who have received bisphosphonate at some point in their life.



**Figure 4.**

Cross sectional BMI for participants in the cohort plotted on the CDC growth curves. Open circles represent individuals who were naïve to bisphosphonate treatment while black circles represent individuals who have received bisphosphonate at some point in their life.

**Table 1**

Characteristics of individuals with OI enrolled in the LCRC

	OI I	OI III	OI IV	OI V	OI VI	OI VII	Unclassified	All
Enrollment number	244	110	150	15	12	5	16	552
Male, n (%)	113 (46.3)	47 (42.7)	66 (44)	5 (33.3)	7 (58.3)	0 (0)	7 (43.8)	245
Female, n (%)	131 (53.7)	63 (57.3)	84 (56)	10 (66.7)	5 (41.7)	5 (100)	9 (56.3)	307
Median age in years at enrollment (range)	13.5 (0–67)	11.0 (0–54)	11.6 (0–63)	12.5 (0–35)	9.9 (2–32)	4.2 (0–20)	23.6 (2–47)	12.2
Race, n (%)								
White	227 (93)	87 (79.1)	127 (84.7)	11 (73.3)	8 (66.7)	3 (60)	12 (75)	475
Black	7 (2.9)	10 (9.1)	14 (9.3)	2 (13.3)	0 (0)	0 (0)	2 (12.5)	35
Others	10 (4.1)	13 (11.8)	9 (6)	2 (13.3)	4 (33.3)	2 (40)	2 (12.5)	42
Family history, n (%)	153 (62.7)	9 (8.2)	44 (29.3)	5 (33.3)	1 (8.3)	3 (60)	7 (43.8)	222